# STUDIES ON FAT EMBOLISM USING IODIZED OIL (MOLJODOL)

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CITATION:

Shiraishi, Sadao. STUDIES ON FAT EMBOLISM USING IODIZED OIL (MOLJODOL). 日本外科宝函 1955, 24(3): 237-256

ISSUE DATE:

1955-05-01

URL:

http://hdl.handle.net/2433/206183

日本外科寶函 第24卷 第3号

ARCHIV FÜR JAPANISCHE CHIRURGIE

XXIV. BAND, 3. HEFT, 1. MAI, 1955.

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# STUDIES ON FAT EMBOLISM USING IODIZED OIL (MOLJODOL)

by

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(Received for Publication March 10, 1955)

## INTRODUCTION

Since Zenker described the fat embolism in the lung in 1862, many researches have been made on this subject. Wilms [2] and Fritzsche [2] re of the opinion that the fat granules are mainly carried via venous system, while Aberle, Fuchsig, Lehmann[1], Hoore, Ribbert [3] and others consider the route via lymphatic system. As the cause of the fat embolism, fracture or commotion of the bone, ether anesthesia[1], aseptic bruising of the tissue, metabolic disturbances, burns etc. have hitherto been reported.

Intending to clarify some aspects of the development of the fat embolism originating from the bone marrow, I traced on X-ray films the distribution of the iodized oil which had been injected into the bone marrow of rabbits.

## EXPERIMENTAL METHOD AND RESULTS

Relatively young rabbits of 4 to 6 months after birth (body weight : 1500-1800 g) were subjected to experiments, in order to minimize the possible embolism of normal intramedullary fat of rabbit which cast no shadow on X-ray films. 40 % moljodol (Dai-Ichi) was used as the iodized oil preparation.

A) Group I : Rabbits Being Injected Moljodol into the Bone Marrow

Through a boring hole of 1. 1 mm in diameter a blunt injection-needle with inside diameter of 0.8 mm was nserted into the bone marrow. After the needle was left in place, being fixed to the bone, for 3-5 days, until the damaged blood vessels in the bone marrow were barely repaired, 0.15-2.0 cc of moljodol was injected. To prevent the escape of moljodol after removing the needle, the boring hole was stopped up with the bone wax.

i) Rabbits being injected moljodol into the femur.

When a large dose of moljodol (2.0 cc) was injected, animals died within several miuutes. In these animals, moljodol was demonstrated by X-ray in the lungs, heart, inferior caval vein, renal vein and in hepatic vein (Photograph I-IV) and fat granules could actually be found in those blood vessels at autopsy. Though there were exceptional cases with the survival for more than 26 hours, rabbits being injected a relatively small dose (0.8~1.0 cc) died usually in 5-12 minutes. However, following the injections of a small dose (less than 0.4 cc) all rabbits survived for more than 3 hours. These animals were killed by opening the thoracic cavity and roentgenographs of their internal organs were taken. None of these animals showed the clinical signs[4) 12) 15)] or roentgenographic manifestations suggesting the cerebral embolism.

(Photograph I) : Rabbits being injected 2.0 cc of moljodol into the bone marrow of the left femur. Movements of moljodol from the injected region via venous system were verified by the shadows on a X-ray film of the femoral, caudal portion of the inferior caval, renal (retrograde) and hepatic (retrograde) veins and highly distended subphrenic portion of the inferior caval vein. Besides, moljodol flowing retrogradely to the periphery after having entered into the local subcutaneous veins and also the oil having oozed out of the trochanter region into the neighboring soft tissue were recognized.

(Photograph II) : The left femur was broken in a dying stage of the same rabbit as in Photograph I. The femoral vein is bent because of the shortening of the extremity. As a large dose of moljodol has been forced into snbcutaneous veins at the moment of fracture, they are more clearly and extensively demonstrated than in Photograph I. Moljodol becomes plentiful within the pelvic and prevertebral veins, and a collateral path (the ascending lumbar venous system)——later to be described in detail——is also recognized. Bifurcating pulmonary artery and the right heart are clearly seen, too.

(Photograph III) : Roentgenograms of internal organs. Moljodol is clearly recognizable in the right heart and the lungs and is distributed dot-like in the liver. In the kidney, moljodol is found more abundantly on the film than in the life-time, presumably due to the further ascending of moljodol from the femur before death.

(Photograph IV) : The roentgenogram of another rabbit taken after the injection of 1.5 cc of moljodol into the left femur : (i) the left renal and hepatic veins, as well as distended subphrenic and undistended thoracic portion of the inferior caval and intercostal veins, the heart and the pulmonary arteries can be apparently distinguished, (ii)the positional relationship between the vertebra and the venous system, particularly the curving of the phrenic portion in sideview, is definitely shown.

(Figure I) : Three hours after moljodol had been injected 0.2 cc each into the femurs on both sides (1, 1'), the right femur was fractured. Immediately after the fracture, moljodol within the right femur is reduced in amount as compared

with 1 and 1', presumably as the result of having moved into the blood circulation, In the intact left femur, though the shadows of moljodol have become somewhat denser and smaller in size due to the surface tension of the oil, there can be recognized no definite quantitative differences between before and after the fracture on the opposite side (2 2'). After three and a half hours, no further quantitative changes can be detectable in the two femurs, except for a little more tendency of the shadows to become smaller in the left femur (3 3') After six and fifteen hours respectively, moljodol in the left femur remains unchanged, while that in the right diminishes very slowly by moving into the blood flow (4 4' 5, 5'). After twenty-six hours, the remaining of moljodol in the fractured right femur is only slight, whereas that in the left is unaltered (6, 6'). Though in a small amount, moljodoj can be demonstrated in the lungs of this rabbit (7).

From these facts, it can be said that the portion of moljodol which has not entered into the blood stream at the moment of fracture, remains in the bone marrow for a long time, although it moves into the blood quite slowly. In other words, the quick mobilization of moljodol into the blood circulation takes place only at the moments of injection and of fracture.

After the bone has been deprived of the surrounding fat tissue thoroughly and kept in warm water of 38° C for 10 minutes until no more oil drops come out, the bone is broken in fresh warm water, and then there appear oil drops again. It is, therefore, certain that the fat in the bone marrow is freed in case of fracture. Changes similar to those in the femur above mentioned are also found in cases of the injection of moljodol into the humerus (Figure V-1, 2, 3, 4)

(Figure II) : Thirty minutes after moljodol had been injected 0.15 cc each into the right femur in two rabbits (1, 1') the femur of the one rabbit was fractured. After three hours, both rabbits were killed and the X-ray examination of the lungs was done. There are no marked differences in the amount of moljodol demonstrable in the lungs between the two (2, 2').

It may be cousidered (1) that the amount of moljodol being mobilized into the blood is too small to prodnce any chahges in the shadows on X-ray films of the lungs or (2) that moljodol being once embolized in the lungs has been freed due to the dilatation of pulmonary vessels in response to the pain and other factors at the site of the fracture.

(Figure III) : To examine the validity of the latter assumption, similar experiments were done in two rabbits generally anesthetized with evipau. But, no marked differences were recognized between the lungs of the two on X-ray films (1, 1', 2, 2'). Also in experiments with rabbits being injected adrenalin, there were no marked differences in the moljodol content of the lungs as compared with that of non-injected ones (Figure VIII-1, 2).

Thus, it may be concluded that, because the total amount of moljodol injected is small, also the amount of moljodol being mobilized into the blood at the moment of fracture is too small, as compared with that having been embolized in the lnngs before fracture (i. e. at the time of injecting moljodol into the bone marrow), to

produce any difference in the shadows of the lungs between before and after the fracture. However, the mobilization of moljodol into the blood circulation may be roughly estimated by the reduction in the amount of the oil in the bone marrow.

(Figure IV) : Experiments were done to examine whether some external forces other than the fracture, such as the blow or the bending, might result in the fat embolism originating from the bone marrow. After 0.2 cc of moljodol has been injected into the right femur (1), the forced dendings by the fingers of the examiner or the blows by a wooden mallet are delivered on the bone. There are found no chauges in the distrib tion of moljodol in all roentgenograms immediateyl (2), three hours (3), seven hours (4), ten hours (5) and twenty hours (6) respectively after the trauma. In other words, moljodol in the bone marrow does not enter the blood circulation following the bendings or the blows only.

It has been thus made certain that moljodol may be mobilized from the femur into the blood stream of the inferior caval venous system mainly at the moments of the injection and of the fracture To examine if there might be some other collateral paths, the inferior caval vein was ligated at the level 3 cm cranial of the bifurcation and 4 cc of moljodol was injected into the right femur of a rabbit. The rabbit became short breathed in three minutes and died five minutes after the injection.

(Photograph V-1') : The shadow of moljodol, 4×6 mm in size and oval in shape, stagnating in the inferior caval vein near the ligature is seen. The lumbar ascending venous system (which ascends on the right side of the inferior caval vein, communicating with the upper portion of the latter), the right (very feeble) and the left bdominal wall vein are also demonstrated. Though moljodol is already recognizable in the lungs and the heart in a large amount, the subphrenic portoin of the inferior caval vein contains only a small amount of the oil.

(Photograph V-1, 2) : The lateral view of the same rabbit. The abdominal wall veins are situated anterior to and ascending lumbar venous system posterior to the globose shadow of the ligated inferior caval vein. These situational relationships coincide with macroscopic findings in a dead rabbit, which has been injected methylene blue solution into the femoral vein with pressure after the ligation of the inferior caval vein. Moljodol is also seen on X-ray film of the chest clearly and in a large amount.

(Photograph VI) : Post-mortem roentgenogram of the sane rabbit (after being fractured). The right atrium and ventricle of the heart, pulmonary artery, subphrenic portion of the inferior caval vein, renal veins on both sides are seen. Moreover, the abdominal wall veins and the lumbar ascending venous system have appeared more clearly than in the preceding photograph. The ligated part of the inferior caval vein is situated in the pelvic cavit and intrapelvic veins are also clearly seen. Thus the collateral accessory venous paths do exist, but it seems not to be utilized in the ordinary condition.

ii) Rabbits being injected moljodol into the humerus.

(Figure V) : Almost the same results were obtained following the injection of

0.5 cc of moljodol into the humerus as in cases of the intrafemoral injection. Moljodol being injected into the bone marrow is clearly seen in the diaphysis and the epiphysis near the humeroscapular joint (1). Immediately after the fracture, moljodol in the diaphyseal portion disappears (by moving into the blood) and the one in the epiphysis somewhat diminishes (2). After three hours, reduction in the amount of moljodol in the epiphysis becomes more apparent (3). After six hours, the roentgenogram is nearly the same as 3 (4).

By this time, moljodol is apparently seen in the lungs. It is, therefore, evident that moljodo being mobilized into the blood has been embolized in the lungs (5). In general, moljodol in the humerus is reduced a little more rapidly following fracture than that in the femur. Similarly to the experiments in the femur, no clinical signs or roentgenograms suggesting the cerebral embolism are observed.

iii) Histologic examinations (Photograph VII, iii, 1, 2, 3, 4, Sketch)[4]

Histologic sections were prepared in the following way. Fixed in formalin, decalcified in 5 % formic acid under low pressure, embedded in carbowax, and stained with Sudan III and hematoxylin-eosin.

Photographs iii-1, 2 show histologic features of a removed femur, into the bone marrow of which moljodol has been injected, and black granules (A) in intra-o seal blood vessels are moljodol (iii-1, 2) and granules (B) are blood cells (iii-1' 2, 3, 4). Considering from these histologic findings, moljodol flows out of the bone marrow into the femoral vein through intraosseal blood vessels and reaches the lungs. That the oil can also ooze out of the bone in the epiphyseal portion by some route, is easily supposed from the shadow in the trochanter region in Photographs I and V.

B) Group II : Rabbits Being Injected Moljodol in the Outside of the Bone

(Figure VI) : When injected extratibially avoiding to injure nearby veins under the X-ray control, moljodol is seen to stay there in the soft tissue (1). After three hours (2), the tibia was fractured at the site near the deposition of moljodol. Thereafter moljodol ascends dispersely in the soft tissue up to the suprapatellar region (3). This rabbit survived for nine days. The roentgenogram taken on the day of death shows the ascendence of moljodol towards the hip joint (4). Autopsy revealed the pleural adhesion and pneumonic changes, but no shadows in the lungs can be seen on the X-ray film (5).

(Figure VII) : It may be recognized that moljodol which has flowed out through the trepan hole moves towards the inguinal region (1). After three hours, a portion of moljodol gathers apparently in the inguinal region, but the oil still remains largely deep in the soft tissue at the site of injection (2). After twenty four hours, moljodol staying in the latter region looks like the one in the Figure VI-4 (3). These experiments show the impossibility of driving the subcu aneously injected moljodol directly into the blood stream.

(Figure VIII) : 0.2 cc of 0.1 % adrenalin was injected subcutaneously in a rabbit. Five minutes later, the rabbit and another control rabbit were injected intravenously each 0.1 cc of moljodol. The two animals were killed thirty minutes

thereafter. Post-mortem X-ray examination reveals no marked difference in the amount of moljodol in the lungs between both rabbits (1, 2).

C) Group III : Rabbits Being Injected Moljodol Intra-Arterially

i) Rabbits being injected moljodol into the internal carotid artery.

When 0.3-0.5 cc of moljodol is injected into the common carotid artery ligating the external carotid, a large percentage of moljodol passes through the brain and reaches the lungs (photograph VIII-2). In the brain, moljodol is demonstrated mainly in meninges (Photograph VIII-1) and scarcely within the cerebral substance.

Slices of the brain of 2.5 mm in thickness were made in the frontal direction and the X-ray photographs were taken. A very scarce amount of moljodol is recognized within the cerebral substance (Figure X-1, 2).

All these rabbits did not die immediately following the injection, but survived only for five minutes to five hours in the state of coma after having developel convulsive seizures and exophthalmos.

ii) Rabbits being injected moljodol into the femoral artery.

In roentgenogram immediately after the injection of 0.2 cc of moljodol into the left femoral artery, moljodol is recognized in arteries of the leg (Photograph IX-1, Sketch-1). One hour later, moljodol can no more be found in the arteries (Photograph XI-2, Sketch-2) and already has reached the lungs (Figure IX-1). This rabbit was alive on the next day and devoid of any signs of the circulatory disturbance.

The results above stated may be summarized as follows.

a) At the moment when moljodol is forced into the normal bone marrow, some portions of the moljodol soon reach the lungs mainly via venous system [17], producing the embolism, and the other portions remain in the bone marrow for a comparative long time. The same thing occurs also at the moment when the bone with moljodol previously injected is broken. (No cases suggesting the brain embolism were observed.) The amount of moljodol embolized in the lungs does not undergo a noticeable change by painful stimuli (or by receiving adrenalin). Moljodol remaining in the bone marrow without entering the blood circulation immediately after the injection stays there for a comparatively long time without suffering marked changes thereafter. Except for the fracture, external forces acting on the bone such as the bending or the blow do not change the distribution of moljodol, too.

b) Moljodol being injected into the subcutaneous tissue does not directly enter the blood circulation, even when the neighboring bone is broken, but seems to enter the lymphatie nodes through lymphatic vessels within the tissue.

c) Moljodol being injected intra-arterially reaches the lungs after passing through peripheral capillaries in a comparatively short time. In the brain, the embolism occurs mainly in the meningeal arteries, but rarely in the intracerebral ones.

## Comment

Judging from my experimeutal results, the opinion of Ribbert and others [12) 16)]

that the fat embolism is caused mainly by the commotion of the bone may not be convincing and the fracture must be the main cause as Frischmuth and Bergmann [13] assert. When a bone is fractured, a certain amount of fat in the bone marrow may be instantly forced into the simultaneously destroyed and uncontractile veins in the bone marrow and then reaches the lungs to be embolized After the fractreu has taken place, the fat in the bone marrow seems to be continuously mobilized into blood stream very slowly in a comparatively long time and to reach the lungs via veins. Therefore it may be a matter of course that Halm and Bürgen [9] have found the fat embolism in the lungs in almost all of one hundred patients with fractures. It may also be convincing that, as Bergmann [9] or Payr [8] states, the fat embolism is most liable to occur when the bone being rich in fat is bruised.

The intrapulmonarily embolized fat does not further move in the ordinary conditions. However, in the particular conditions (e. g. after the injection of drugs dilating the contracted pulmonary vessels ——histamine, eupaverine, decoline, etc. or of those turning the fat into emulsion), it passes through the lungs and enters the arterial system. (Direct entry into the arterial system takes place naturally when some malformation, such as the insufficient closure of the foramen ovale [15] etc., exists in the heart.) The fat entering the arterial system passes rather easily through capillaries in extremities and internal organs. Therefore, the rarity of the death resulting from the cerebral embolism in cases of fracture of extremities may be easily understood. In fact, Nils, Backen and Gröndahe [4] have reported that 57 out of 69 deaths in 1026 cases of fracture are due to fractures themselves or to concomitant head injuries and only one of the remaining 12 deaths is the sequel of the cerebral embolism.

## SUMMARY

1) Studies concerning the fat embolism have been performed using the iodized oil (Moljodol—Dai-Ichi).

2) At the moment of the fracture, the fat in the bone marrow is mobilized into the venous system and reaches the lungs, producing there the fat embolism.

3) The fat entering the arterial system may rather easily pass through capillaries in extremities or in internal organs.

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和文抄錄

# 沃度油による脂肪栓塞の研究

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白 石 貞 男

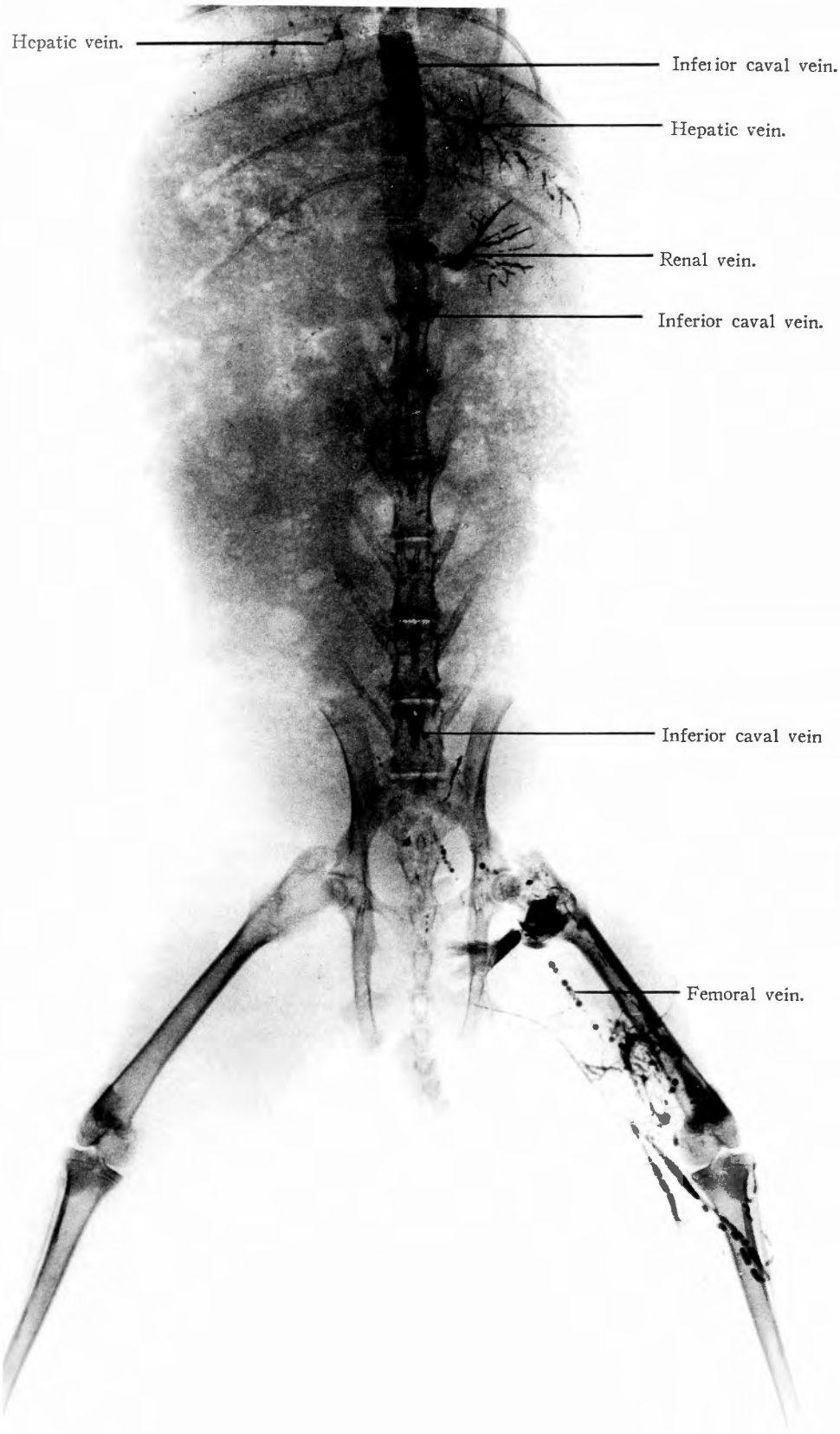
沃度油を兎の骨髄（大腿骨，上膊骨），骨外，動脈内（頸動脈，股動脈）等に注入して之をX線像上で追求し脂肪栓塞を究明し，次の結果を得た．

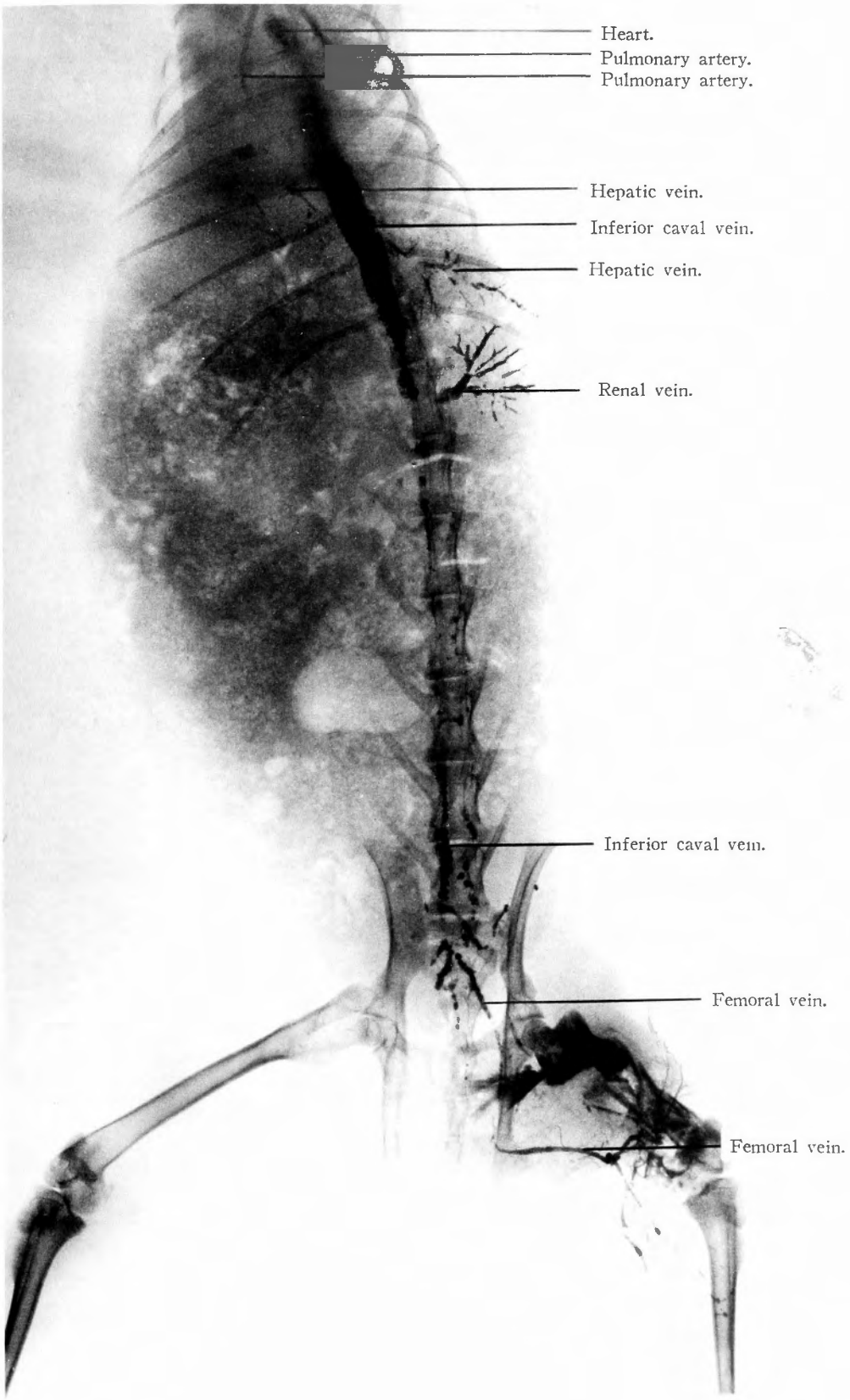
a) 破壊された骨髄内にモルヨドールが圧入されると其の大部分が恰も静脈内注入の如く経静脈的に肺に栓塞を起し，比較的長時間栓塞の状態で存続し疼痛（アドレナリン）等では認められる程の減少を示さない．注入直後に血中に移行する事なく骨髄に残溜したモルヨドールは相当長期に亘り著明な変化を示さず，骨折時に血中に移行する．又之は打撲，歪曲等の外力を骨に加えただけでは著変がない．

b) 皮下組織に注入されたモルヨドールは，其部分の骨の骨折によつても直接血中に移行せず寧ろ組織間隙の淋巴系を経て淋巴腺に入り之より循環系に入ると思われる．

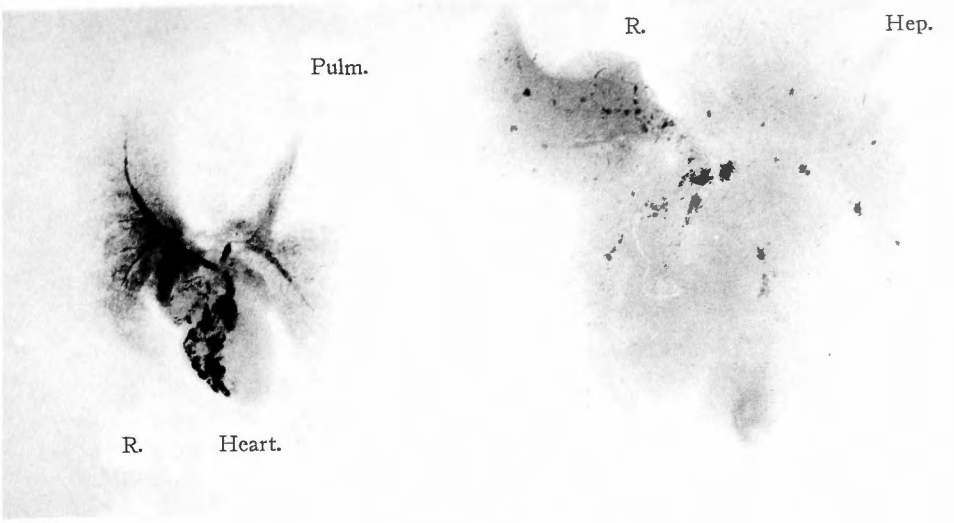
c) 動脈内に注入されたモルヨドールは比較的短時間に末梢の毛細血管を通過し肺に達し，脳に於ては主として脳膜動脈に栓塞し脳質内の栓塞は少量である．

I.

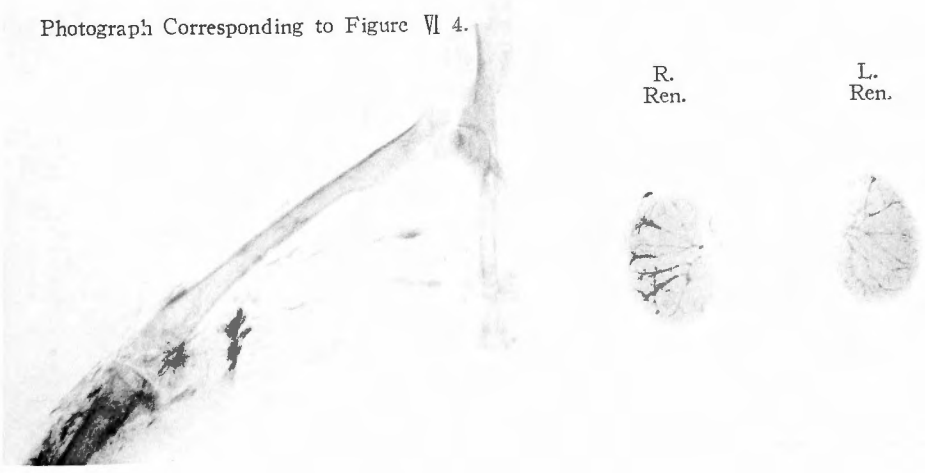

Hepatic vein.
Inferior caval vein.
Hepatic vein.
Renal vein.
Inferior caval vein.
Inferior caval vein
Femoral vein.


Heart.
Pulmonary artery.
Pulmonary artery.
Hepatic vein.
Inferior caval vein.
Hepatic vein.
Renal vein.
Inferior caval vein.
Femoral vein.
Femoral vein.

Ⅲ.



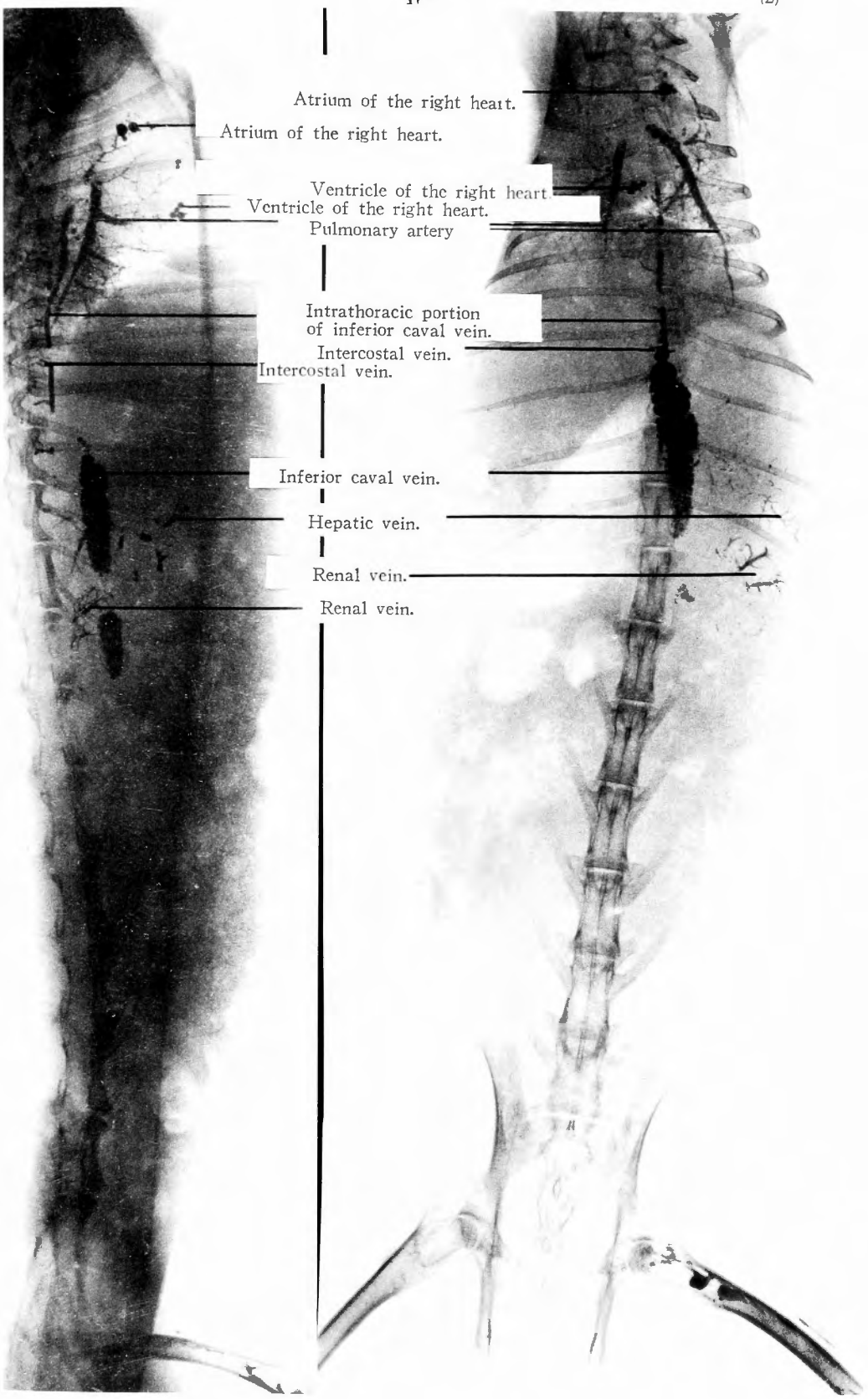

Photograph Corresponding to Figure Ⅵ 4.

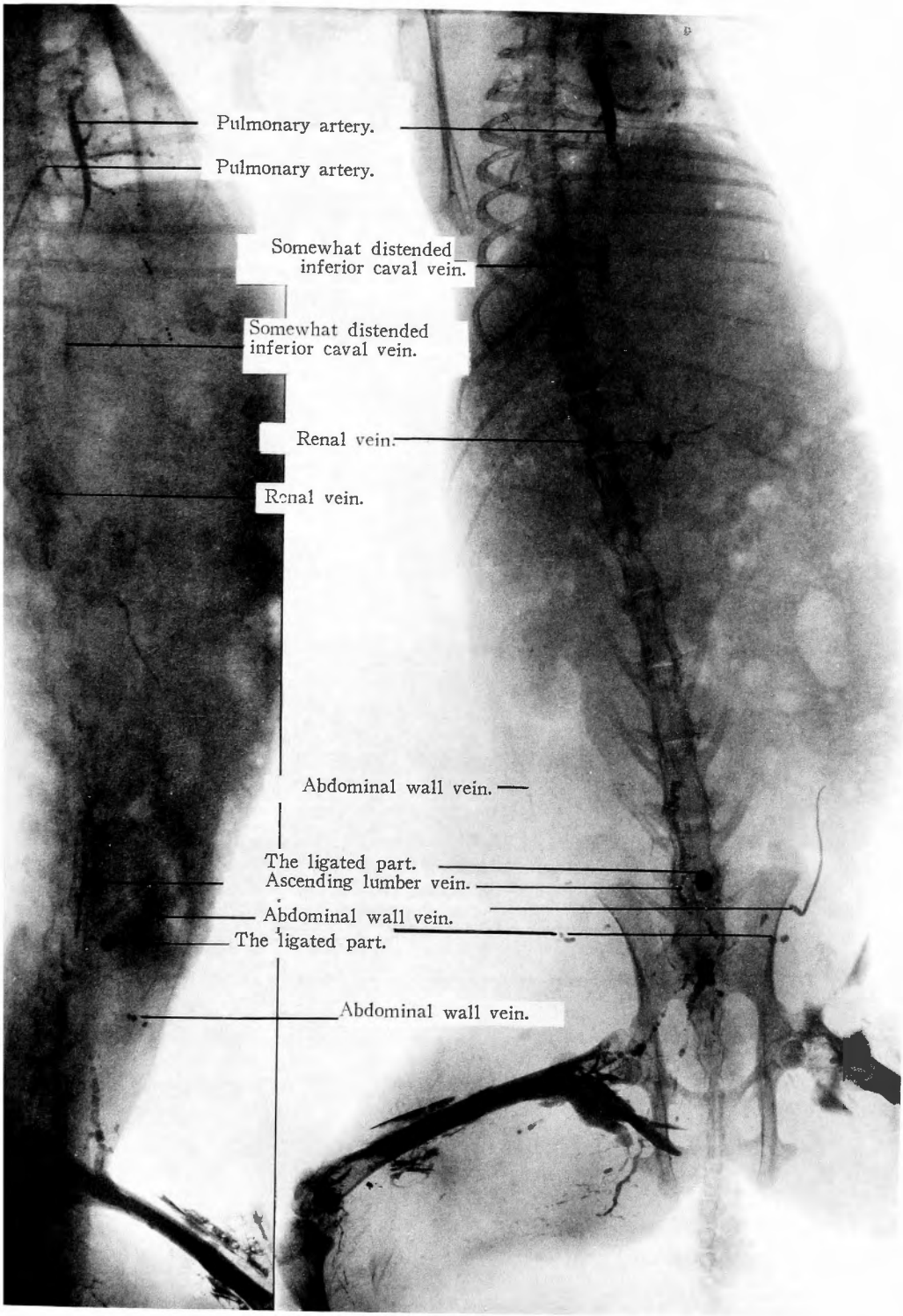


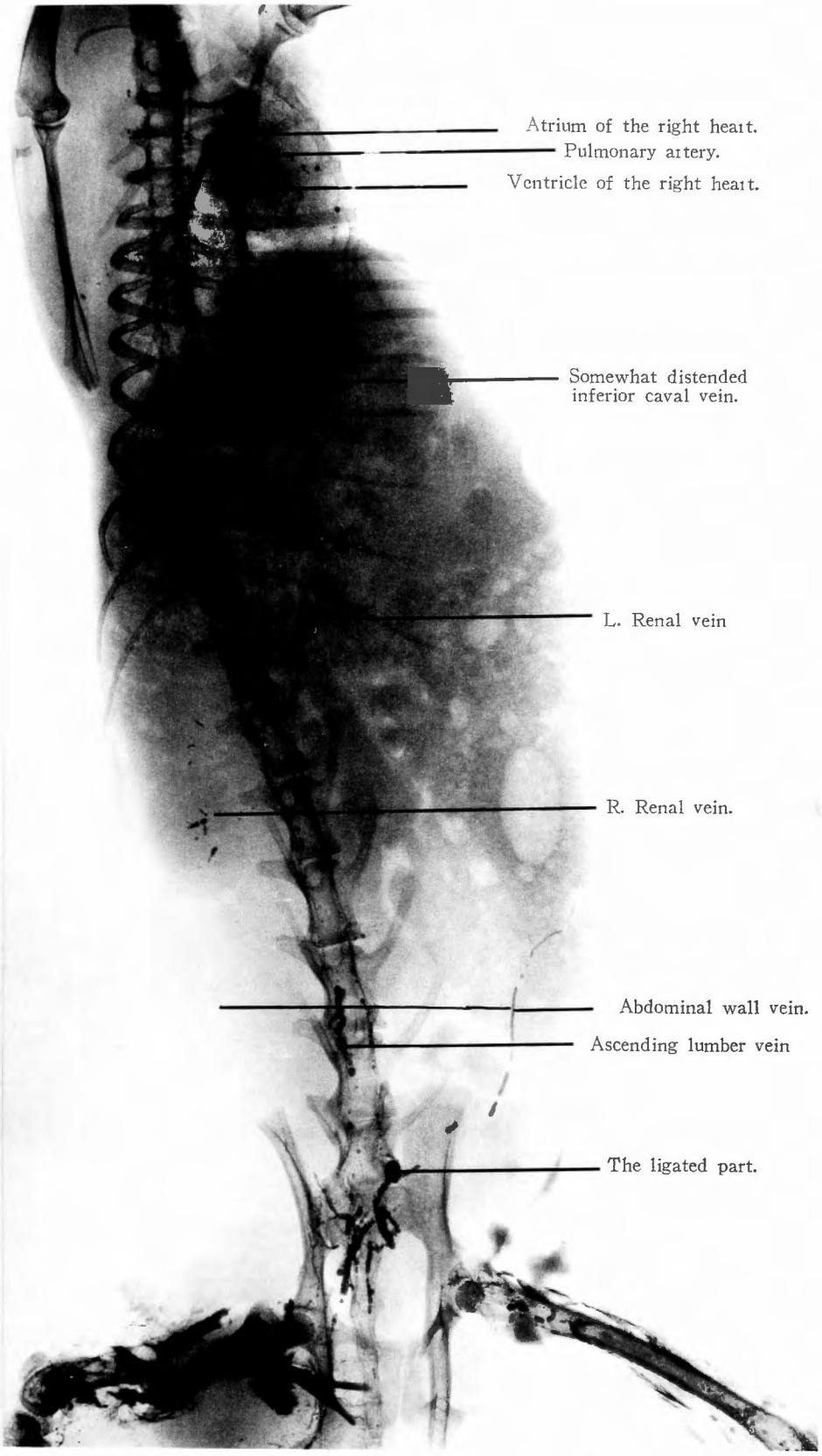
(1)

IV.

(2)

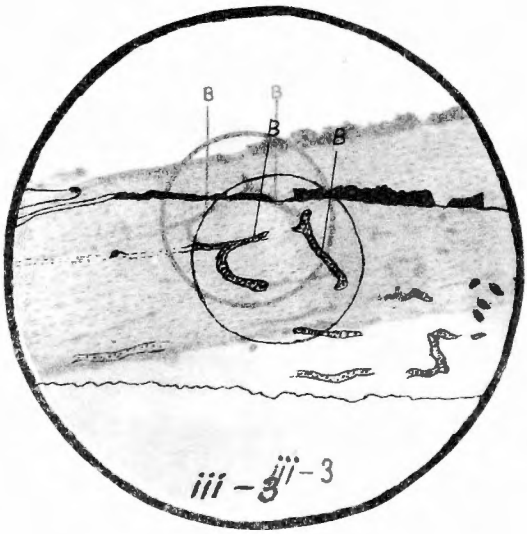

Atrium of the right heart.
Atrium of the right heart.
Ventricle of the right heart.
Ventricle of the right heart.
Pulmonary artery
Intrathoracic portion of inferior caval vein.
Intercostal vein.
Intercostal vein.
Inferior caval vein.
Hepatic vein.
Renal vein.
Renal vein.


Pulmonary artery.
Pulmonary artery.
Somewhat distended inferior caval vein.
Somewhat distended inferior caval vein.
Renal vein.
Renal vein.
Abdominal wall vein.
The ligated part.
Ascending lumber vein.
Abdominal wall vein.
The ligated part.
Abdominal wall vein.

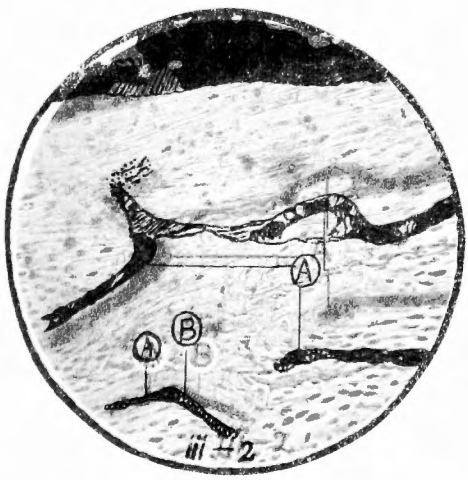

Atrium of the right heart.
Pulmonary artery.
Ventricle of the right heart.
Somewhat distended inferior caval vein.
L. Renal vein
R. Renal vein.
Abdominal wall vein.
Ascending lumber vein
The ligated part.

## Ⅶ. Histologic features of the bone,
(cf. sketch of the photograph)

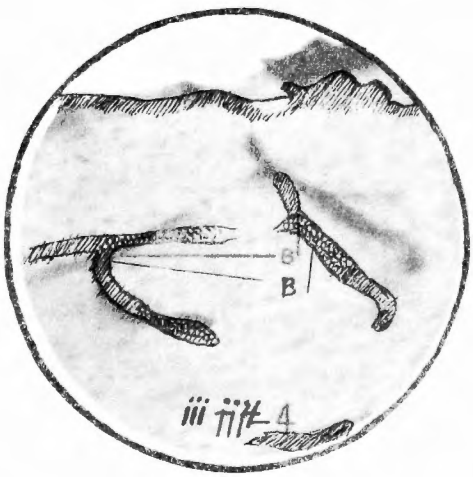

Moljodol has been forced into the bone-marrow.
Low magnification.
A···black (fat granules)
B···gray (blood corpuscles)




Non-injected bone.
Low magnification.
B···Blood vessels containing only blood cells, thongh relatively black stained.



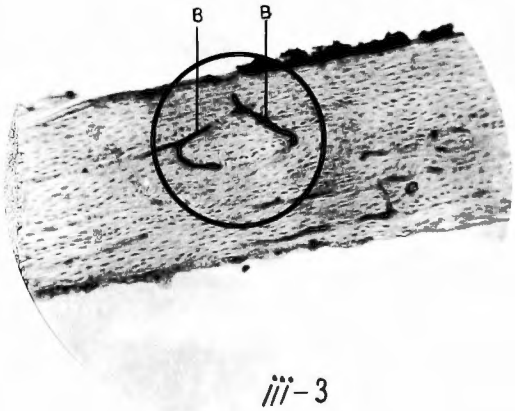

High magnification of the same bone. (cf. iii-1)
A···black and homogeneous (fat)
B···unhomogeneous (blood corpuscles)



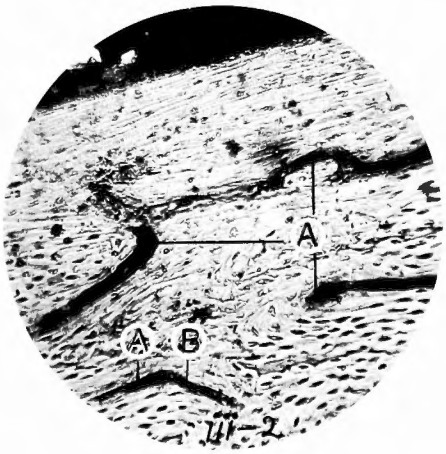

High magnification of the same bone. (cf. iii-3)
B···unhomogeneous (blood corpuscles)

Ⅶ. Histologic features of the bone,
(cf. sketch of the photograph)

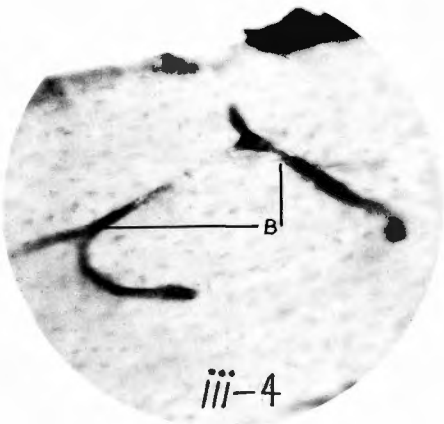

iii-1




iii-3




iii-2




iii-4

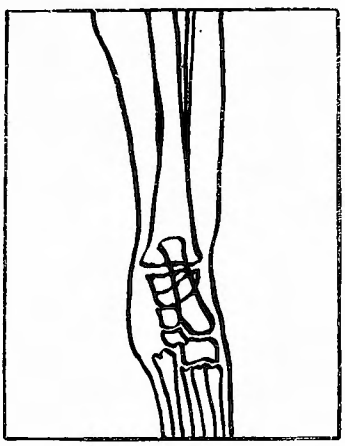
IX. (cf. Figure IX. Heart and lungs)

(2)

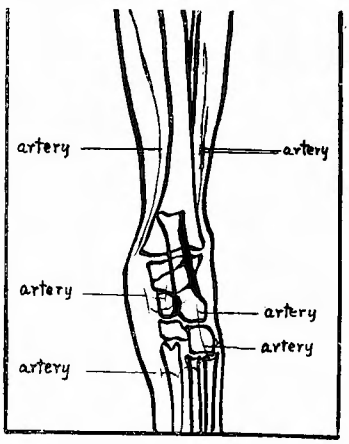
One hour after the intra-arterial injection.
(the same rabbit.)

(1)

Immediately after the intra-arterial injection
of moljodol (0.2cc.)

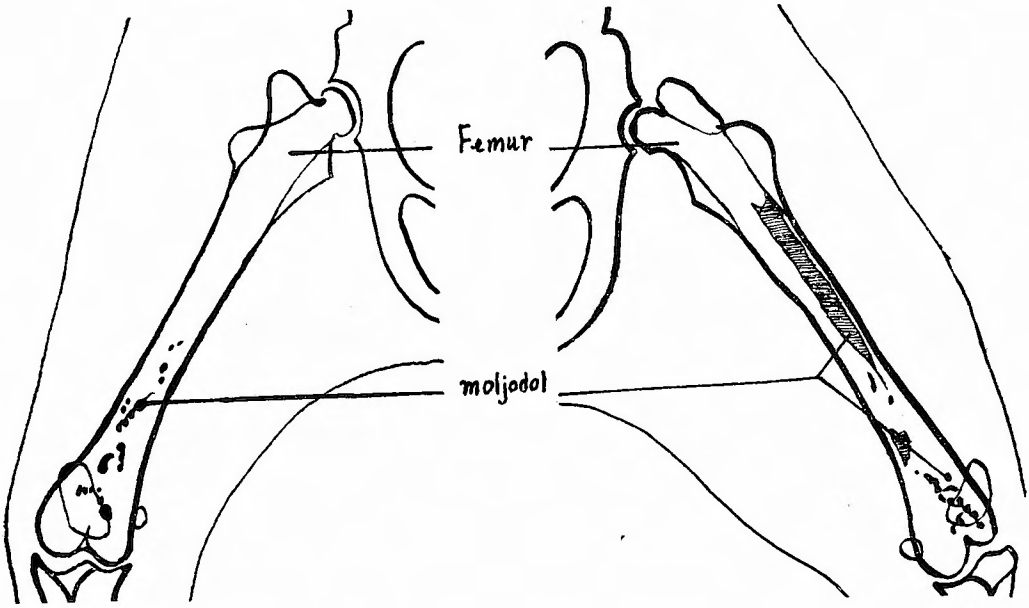


Sketch (2)



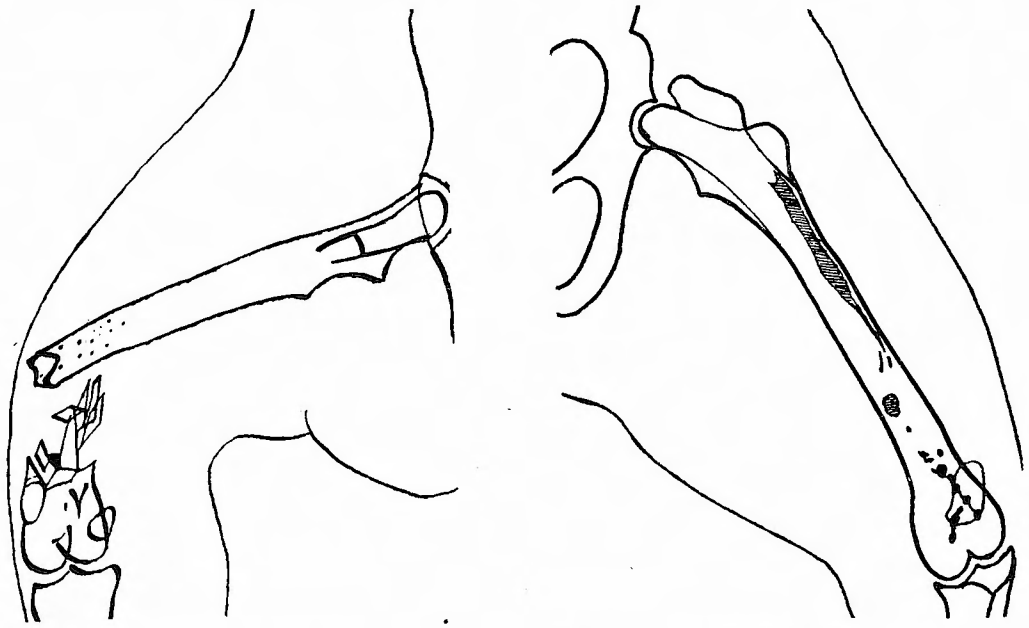

Sketch (1)

**Figure** I. Fracture of the femur.



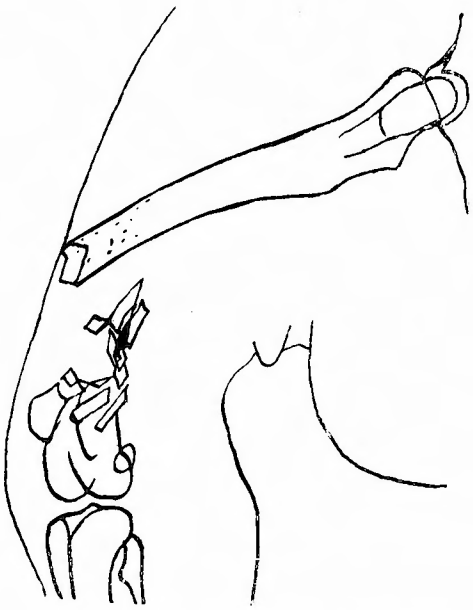

I-(1)′ Just before the fracture. Three hours after 0.2 cc of moljodol was injected.

I-(1) Femur on the other side at the same time as (1)′.

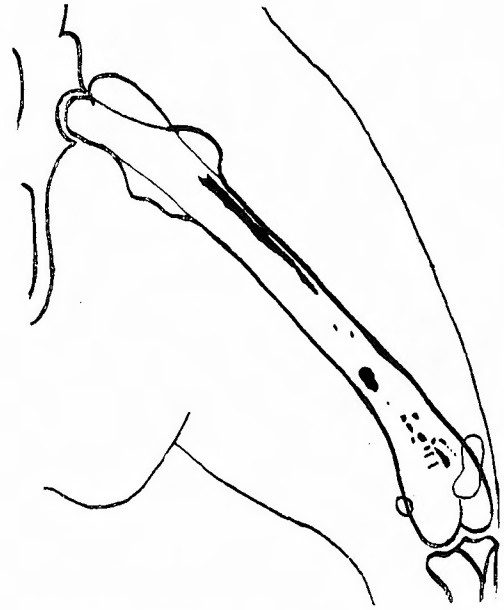


I-(2)′ Immediately after the fracture.

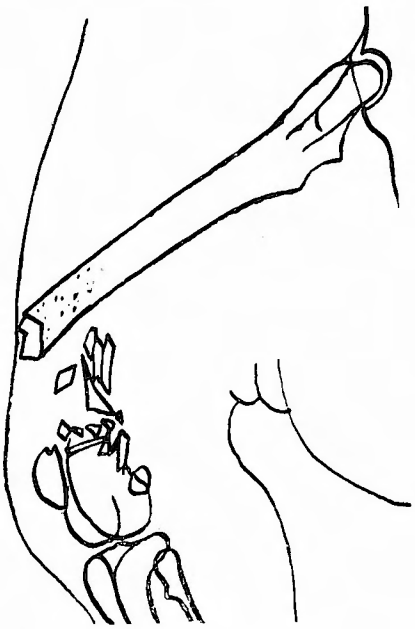
I-(2) The same time as (2)′.



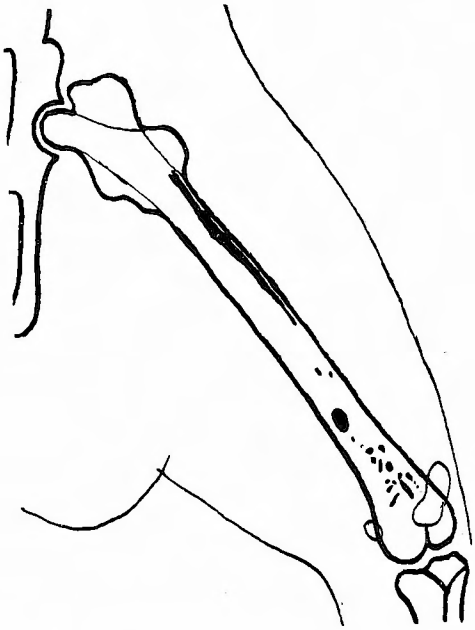
I-(3)′ Three and a half hours after the fracture.



I-(3) The same time as (3)′.



I-(4)′ Six hours after the fracture.



I-(4) The same time as (4)′.

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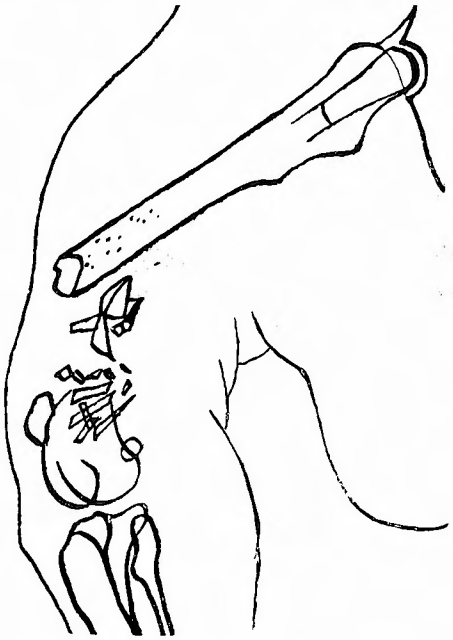
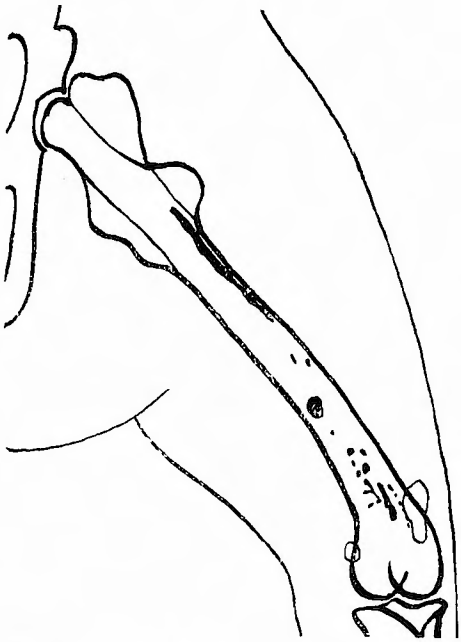
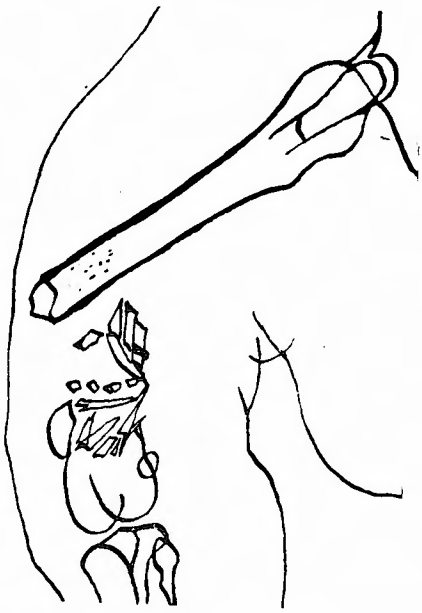


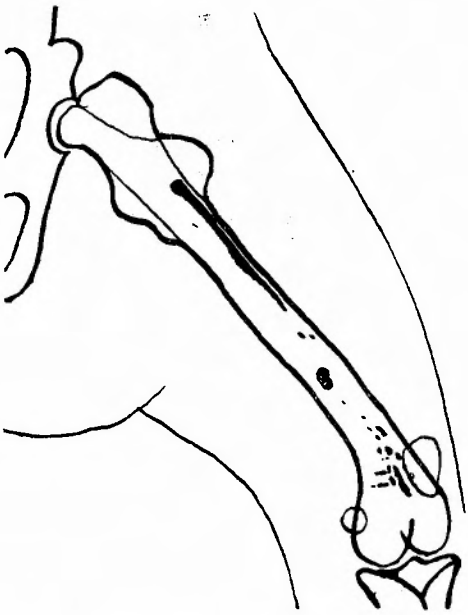
I-(5)′ Fifteen hours after the fracture.



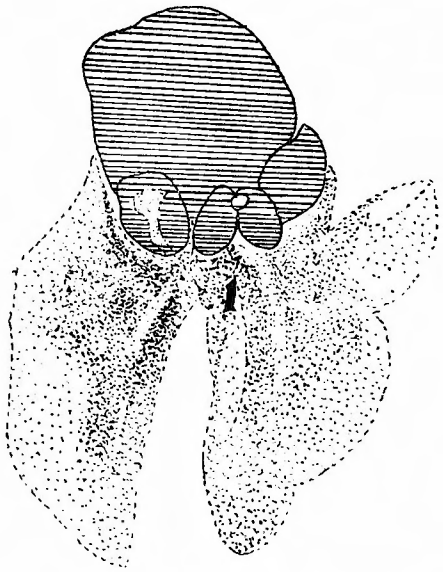
I-(5) The same time as (5)′.



I-(6)′ Twenty-six hours after the fracture.

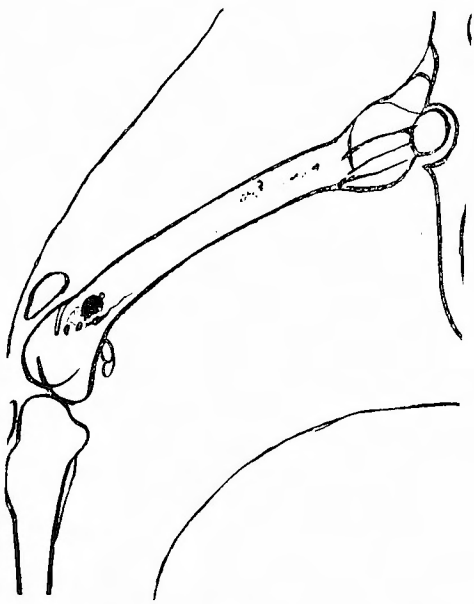


I-(6) The same time as (6)′.

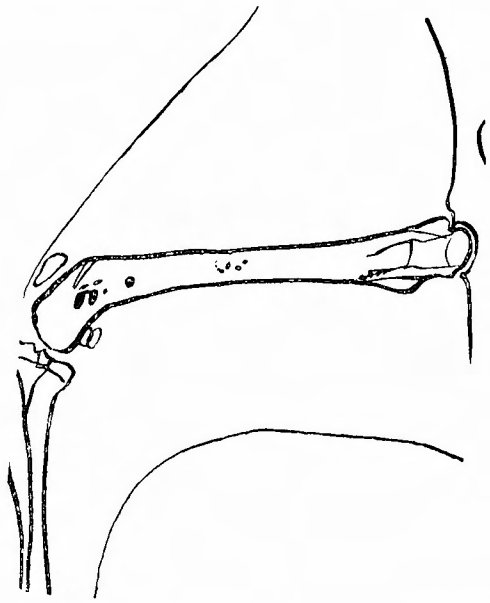


Ⅰ-(7) Heart aad lungs of the rabbit in the figure Ⅰ.

**Figure Ⅱ.** Fracture of the femur.



Ⅱ-(1) Thirty minuts after 0.15 cc of moljodol was injected in one rabbit. No fracture to be followed.



Ⅱ-(1)′ The same time in an other rabbit. Just before the fracture.

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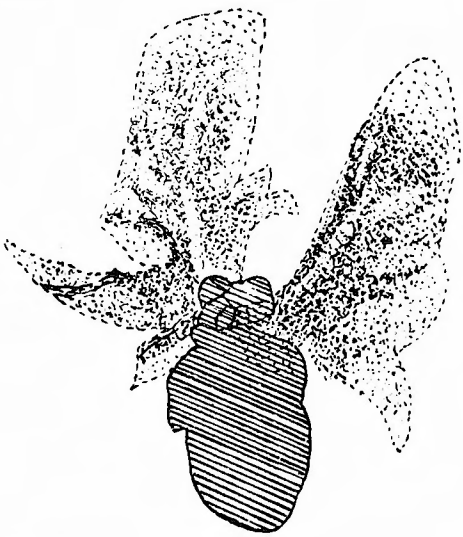
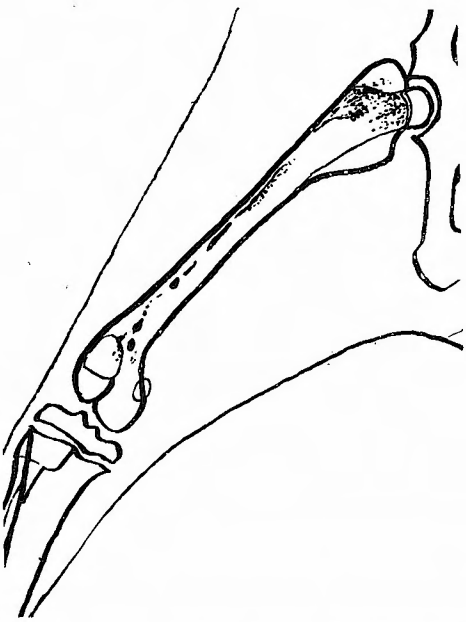
Ⅱ-(2) Heart and lungs of the non-fractured rabbit after further three hours.

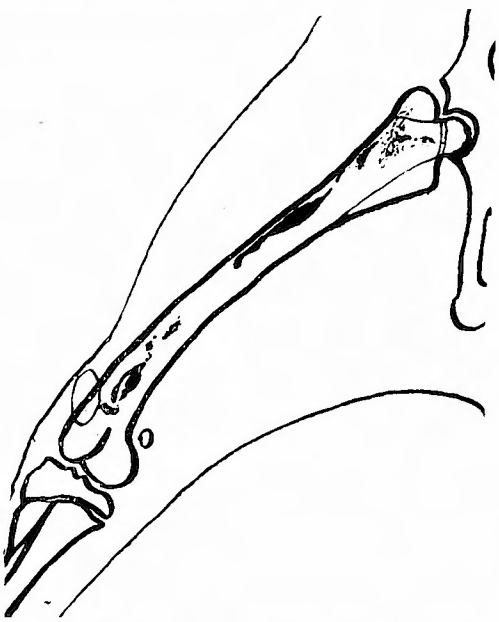


Ⅱ-(2)′ Heart and lungs of the fractured rabbit. Three hours after the fracture.

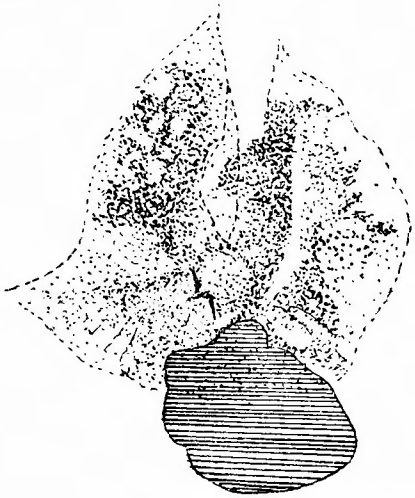
**Figure Ⅲ.** Fracture of the femur under general anesthesia.



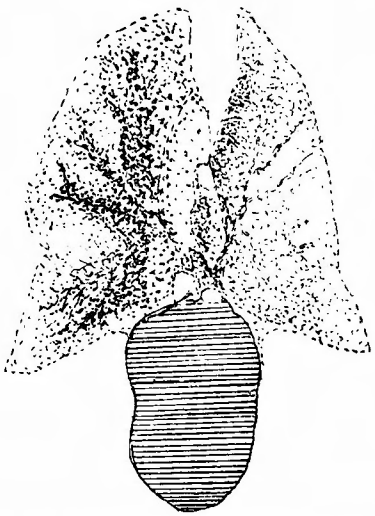
Ⅲ-(1) An intact rabbit is generally anesthetized using 1.0 cc of 10% evipan-nat. after the injection of 0.2 cc of moljodol into the right femur. No fracture to be followed.



Ⅲ-(1)′ The femur of another rabbit will be fractured under general anesthesia after the injection of 0.2 cc of moljodol.

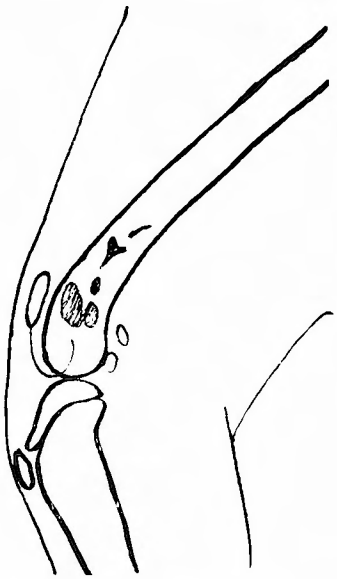


Ⅲ-(2) Heart and lungs of the non-fractured rabbit after three hours.

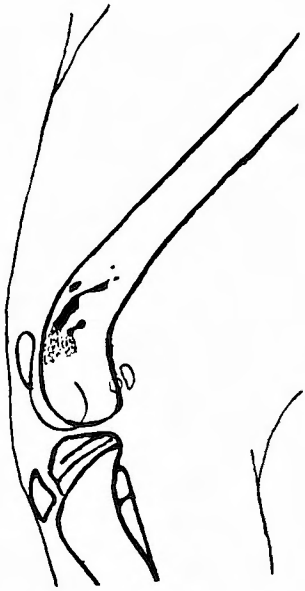


Ⅲ-(2)′ Heart and lung of the fractured rabbit. Three hours after the fracture.

**Figure Ⅳ.** The right femur is bent or given a blow every one hour after 0.2 cc moljodol was injected.

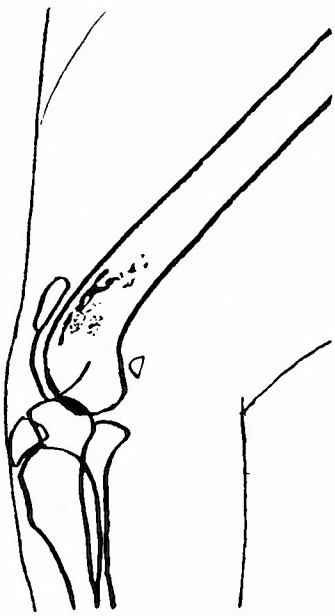


Ⅳ-(1) Before the trauma.

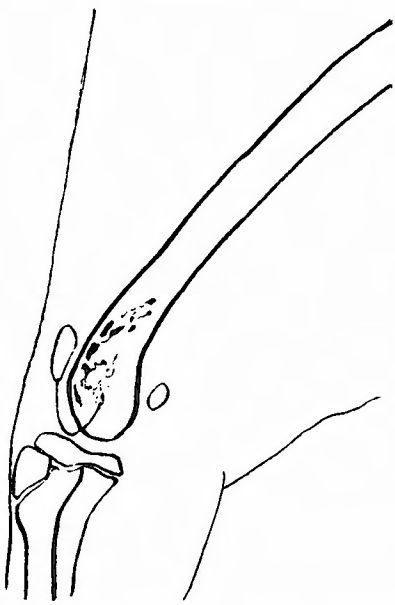


Ⅳ-(2) Immediately after the first trauma.

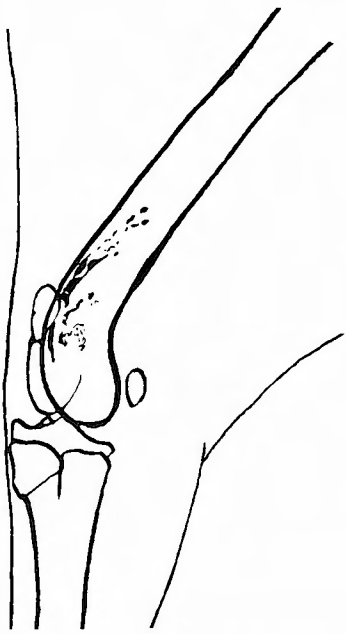
Ⅳ-(3) Immediately after the fourth trauma (after three hours).



Ⅳ-(4) Immediately after the eighth trauma (after seven hours).

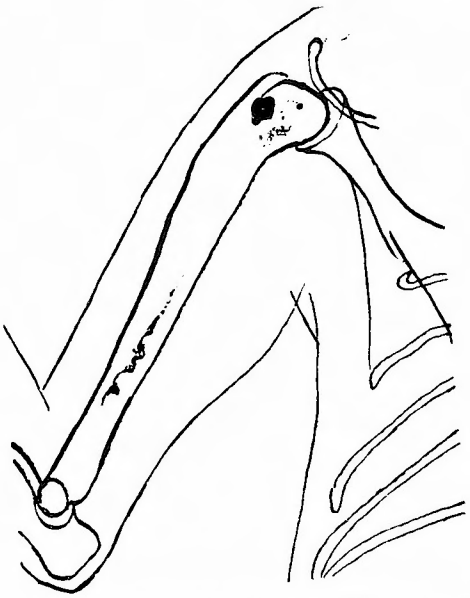


Ⅳ-(5) Immediately after the eleventh trauma (after ten hours).



Ⅳ-(6) Immediately after the twenty-first trauma (after twenty hours).

**Figure V.** Fracture of the humerus.



V-(1) Just before the fracture. Three hours after 0.5 cc of moljodol was injected.

V-(2) Immediately after the fracture.

V-(3) Three hours after the fracture.

V-(4) Six hours after the fracture.

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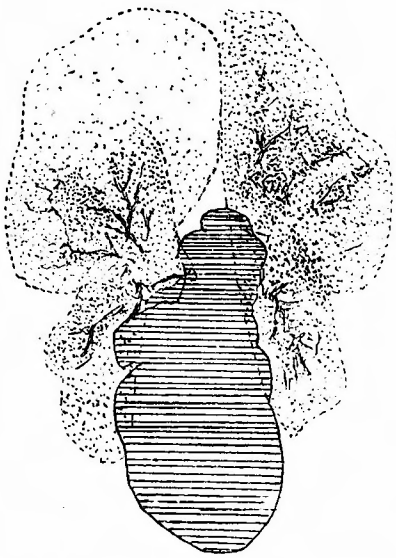
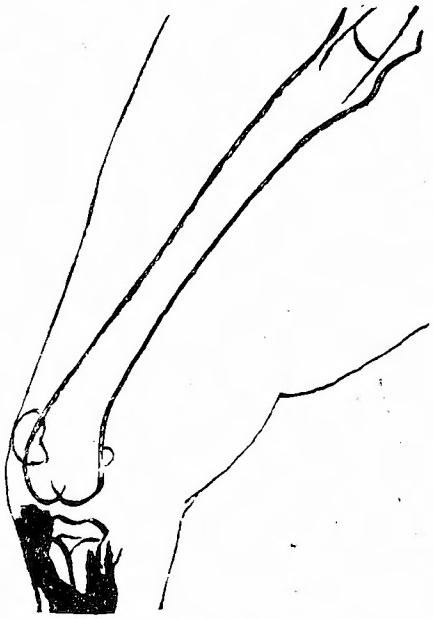
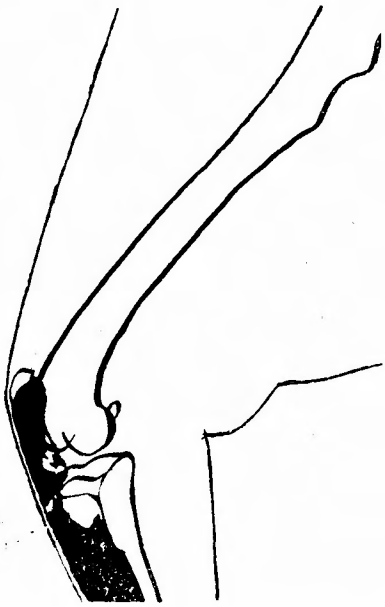
**Figure VI** The extra-osseal injection of moljodol (2.0 cc) under the X-ray control.



V-(5) Heart and lungs of the same rabbit.



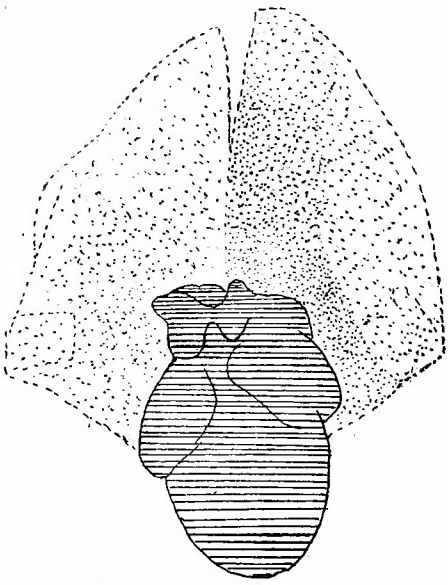
VI-(1) Immediately after the extra-osseal injection.



VI-(2) Just before the fracture. (Three hours after the injection.)

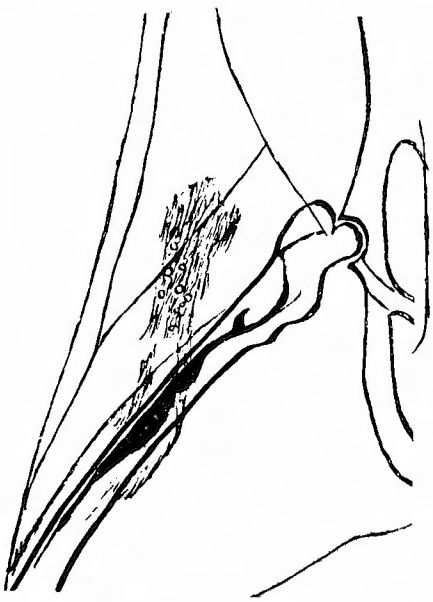
VI-(3) Immediately after the fracture.

Ⅵ-(4) Nine days after the fracture. (cf. Photograph Ⅲ)

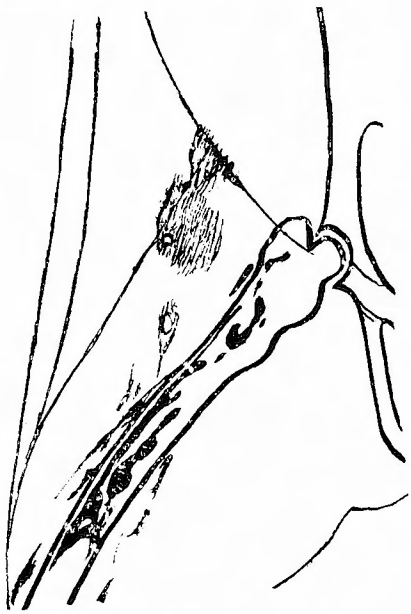


Ⅵ-(5) Heart and lungs of the same rabbit.

**Figure** Ⅶ. Escape of moljodol from the trepan hole into the surrounding tissue. (1.0 cc of moljodol was injected into the bone marrow.)



Ⅶ-(1) Immediate escape of moljodol.



Ⅶ-(2) Three hours later.

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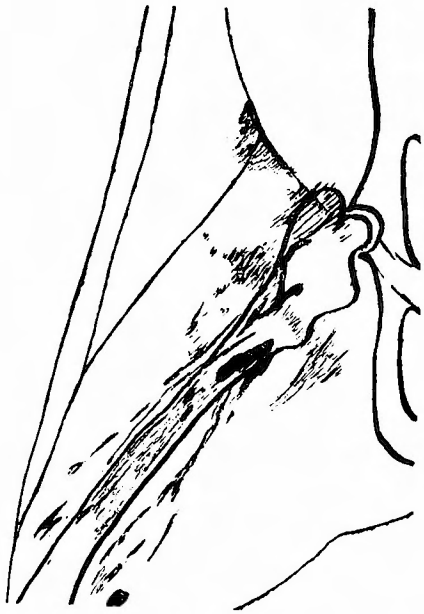
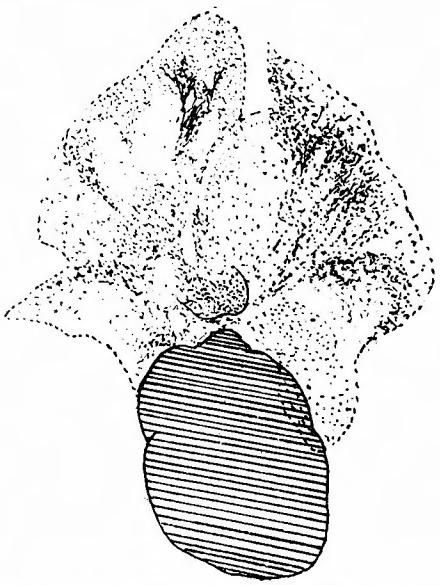
**Figure Ⅷ.** Heart and lungs of the two rabbits having been killed thirty minutes after the intravenous injection of 0.1 cc of moljodol.

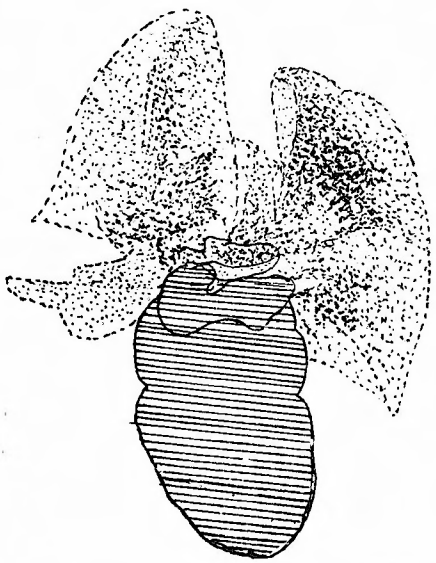


Ⅶ-(3) After twenty-four hours.

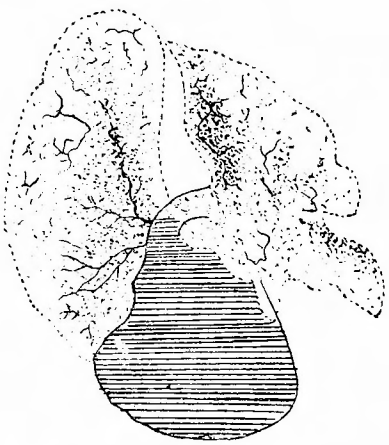


Ⅷ-(1) Heart and lungs of a rabbit. Intravenous moljodol after subcutaneous adrenalin (0.1% 0.2 cc).

**Figure Ⅸ.** 0.2 cc of moljodol was injected into the left femoral artery. (cf. Photo. Ⅸ.)

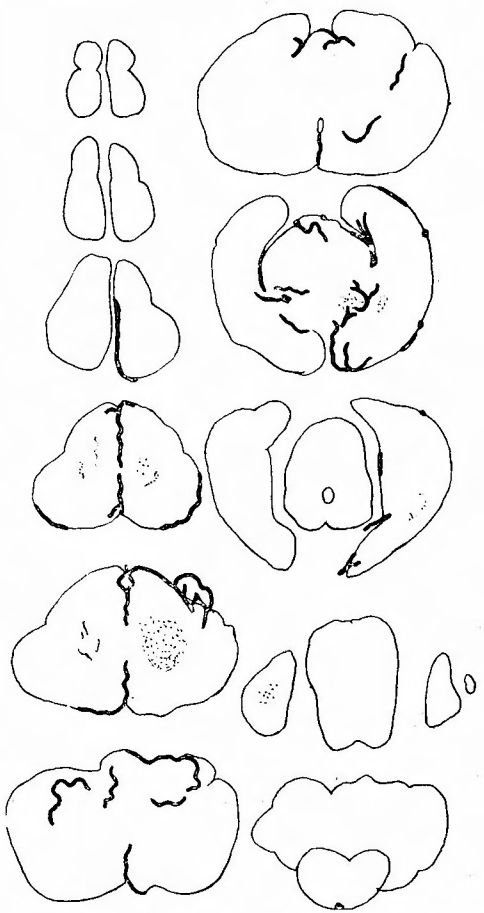


Ⅷ-(2) Heart and lungs of another rabbit. Intravenous moljodol previous adrenaline injection

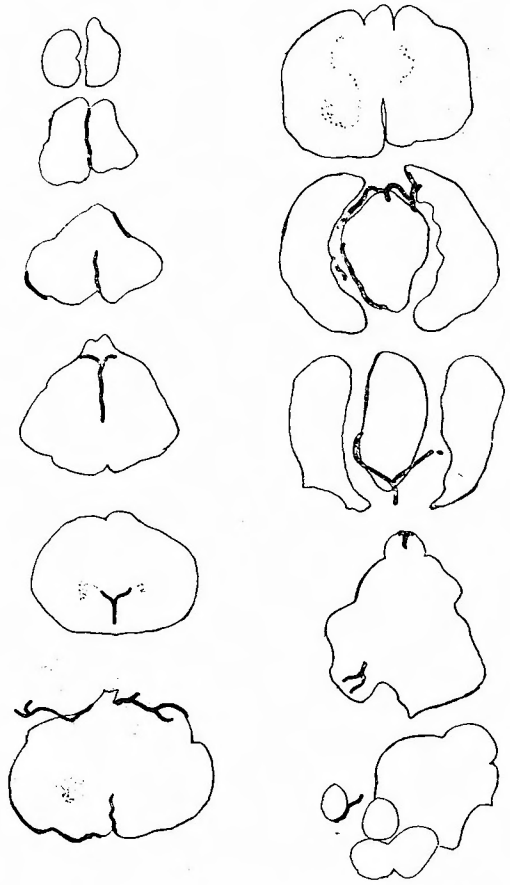


Ⅸ-(1) Heart and lungs.

**Figure X.** Slices of the rabbits's brain in which cerebral embolism has taken place.
(Being injected 0.5 cc of moljodol into the carotid artery.)



X-(1) Moljodol has been injected into the right carotid artery.



X-(2) Moljodol has been injected into the left carotid artery.